VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2021, vol. 92, no. 8, 544–549

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2021.0016

FOXA1 is associated with high tumor grade, myometrial invasion and lymph node invasion in endometrial endometrioid carcinoma

Hülya Tosun Yıldırım[1], Döndü Nergiz[1], Canan Sadullahoğlu[1], Dinç Süren[1], Şenay Yıldırım[1], Işın Üreyen[2], Cem Sezer[1]

[1]*University of Health Sciences, Antalya Education and Research Hospital, Department of Pathology, Antalya, Turkey*
[2]*University of Health Sciences, Antalya Education and Research Hospital, Department of Gynecological Oncology, Antalya, Turkey*

ABSTRACT

Objectives: FOXA1 expression has been demonstrated in several hormone-dependent cancers. However, data are limited concerning the role of FOXA1 in endometrial cancers. The present study aimed to investigate FOXA1 expression via the microarray technique in benign hyperplasia, endometrial intraepithelial neoplasia, and endometrial endometrioid carcinoma. We also aimed to determine whether there were any associations between FOXA1 expression, tumor grade, myometrial invasion and lymphatic invasion.

Material and methods: Paraffin-embedded sections prepared from samples obtained from 114 patients who underwent surgical hysterectomy or curettage were analyzed. Data were retrieved from digitally-stored medical records. Tissue microarrays were prepared from formalin-fixed, paraffin-embedded tissue blocks. Full tumor sections were used for immunohistochemical analysis performed.

Results: Carcinomas with nuclear grade 3 had higher FOXA1 values than others, while grade 2 carcinomas also had higher FOXA1 values relative to grade 1 ($p < 0.001$). FOXA1 values of FIGO stage III carcinomas were significantly higher than others and stage II values were also significantly higher than stage I FOXA1 values ($p < 0.001$). Patients with myometrial and lymph node invasion had significantly higher FOXA1 values than others ($p < 0.001$ and $p = 0.047$, respectively). FOXA1 had 91.30% sensitivity, 63.60% specificity and 77.78% accuracy for predicting the presence of myometrial invasion with a cut-off value of 9.

Conclusions: FOXA1 expression is higher in endometrial endometrioid carcinoma compared to benign endometrial hyperplasia or intraepithelial neoplasia. In patients with endometrial endometrioid carcinoma, high FOXA1 expression is associated with high tumor grade, myometrial and lymph node invasion. However, FOXA1 expression is not associated with lymphovascular or cervical invasion.

Key words: endometrial endometrioid carcinoma; FOXA1; myometrial invasion; lymph node invasion; tumor grade

Ginekologia Polska 2021; 92, 8: 544–549

INTRODUCTION

Worldwide, endometrial cancer is the sixth most common malignancy in women and the most common malignant tumor of the female genital tract [1, 2]. Temporal studies have demonstrated a considerable increase in the frequency of endometrial cancer in developed and developing countries [3, 4]. Endometrial cancer has been generally categorized into two types as the most frequently seen estrogen-dependent endometrial endometrioid (Type 1), and estrogen independent non-endometrioid carcinoma (Type 2) [5]. Benign endometrial hyperplasia (BH) and endometrial intraepithelial neoplasia (EIN) are assumed as histopathological precursors in the development process of endometrioid carcinoma [6]. Mutations in the PTEN, PIK3CA, K-RAS, and CTNNBI and microsatellite instability have been demonstrated to act in the pathogenesis of these tumors [7].

Extended exposure to estrogens is believed to give rise to the development of estrogen-dependent type endometrial cancer. Unopposed exposure to estrogen causes over activation of estrogen receptor α which leads to proliferation via the upregulation of growth factors including EGF and IGF-1 [8]. Several co-activators and co-repressors are known to regulate the activity of the estrogen receptor- α. Forkhead box A1 (FOXA1), a member of the Forkhead Box

Corresponding author:
Döndü Nergiz
University of Health Sciences, Antalya Education and Research Hospital, Department of Pathology, Kazım Karabekir Street, Muratpaşa, 07050 Antalya, Turkey
e-mail: nergizin_d@hotmail.com

transcription factor family, has been reported to increase estrogen receptor- α activity by promoting the binding of estrogen receptors [9]. FOXA1 binding to DNA is known to alter chromatin structure and promote the binding of transcription factors such as estrogen receptor- α. The pathological role of FOXA1 expression has been demonstrated in several hormone-dependent cancers. While the presence of FOXA1 expression has been related to good prognosis in estrogen receptor- positive breast cancers. Conflicting results have been derived from studies investigating its role in prostate cancer [10–12]. In addition to contrasting findings, there is limited data concerning the role of FOXA1 in endometrial cancer and its histopathological precursors.

Objectives

The present study was aimed to investigate FOXA1 expression in BH, EIN, and endometrial endometrioid carcinoma using the microarray technique. Additionally, we aimed to investigate whether any relationship exists between FOXA1 expression and the tumor grade, myometrial, and lymphatic invasion of endometrial cancers.

MATERIAL AND METHODS

The study group was retrospectively selected from 145 patients who had undergone hysterectomy or curettage at Antalya Training and Research Hospital from January 2014 to December 2018. Among these, 20 were excluded due to the lack of viable pathological specimens or insufficient clinical data, while 11 were excluded due to low-quality immunohistochemistry (IHC) results. The remaining 114 were included into the study, of which 45 had undergone simple hysterectomy and 69 had undergone curettage. All patients who had undergone simple hysterectomy (n = 45) had received lymph dissection. Repeat IHC staining was not performed, the available specimens were re-evaluated.

Paraffin-embedded sections were utilized for all measurements; and specimens without sufficient tissue sample and those with histopathologically inconclusive results were excluded from the evaluation. The demographic and clinical data of all individuals were retrieved from digitally stored medical records. Histological grading of the tumors, myometrial, cervical and invasion patterns were determined according to the FIGO (International Federation of Gynecology and Obstetrics) criteria [13]. The study was approved by Ethics Committee of University of Health Sciences, Antalya Education and Research Hospital (11/3, 2018).

Tissue microarrays (TMAs) prepared using triplicate approximately 2 mm tissue cores of tumor samples that provided ideal representation of the tumor and invasion area, were placed into a single recipient paraffin block, using a semi-automated instrument and targeted cores prepared by two experienced pathologists (HTY and CSA). Immunohistochemical analyses were performed using FOXA1 primary monoclonal antibody (at 1:500 dilution, ab173287, Abcam, USA). Sections of 4-µm- thick TMAs were mounted on poly-L-lysine coated slides. Immunohistochemical analysis was performed using BOND-III Fully Automated IHC & ISH Staining System (Leica Microsystems, Germany). Antigen retrieval was performed using FOXA1 primary monoclonal antibody (pH 6) left in citrate buffer for 10-minutes. Sections were exposed to 3% hydrogen peroxide for 5-minutes, incubated with the primary antibody for 30 minutes, using 3,3'diamino benzidine as a chromogen for 5-minutes and hematoxylin as a counter stain for 5 minutes.

All cases were evaluated for nuclear staining status of the tumor cells by the same two experienced pathologists (HTY, CSA). Each specimen was assessed by both pathologists and a consensus result was deemed as the result. Briefly, five fields with at least 100 tumor cells were evaluated. Any intensity of nuclear staining of FOXA1 in ≥ 1% of the tumor cells was considered positive regarding the control sample intensities (prostate cancer cell nuclear staining intensity). As we were focused on determining whether specimens were positive or negative for FOXA1, we did not utilize any specific scoring system. The pathologists were able to reach a consensus decision on all samples; thus, there were no inconclusive results within the final reports. All cases were scored without prior knowledge of diagnosis or pathological stage of tumor. When the staining intensity was weak and deemed as nonspecific, then background staining was not evaluated. TMA cores with inadequate tumor samples for evaluation were not included in the end results. Sections of prostatic carcinoma were used as positive control for FOXA1.

The SPSS version 21 software was used for all analyses. Normality of distribution was checked with the Shapiro-Wilk test. Data were given as mean ± standard deviation (SD) and median (minimum-maximum) where and when appropriate. Comparison of FOXA1 values between groups were performed through non-parametric tests due to limited patient numbers, by the Mann-Whitney U test or Kruskal Wallis test, depending on group count. Post-hoc pair wise comparisons were made by using the Bonferroni correction method. The relationship between age and FOXA1 values was evaluated by calculation of the Spearman Correlation Coefficient. The performance of FOXA1 values for the prediction of myometrial invasion was calculated via Receiver Operating Characteristics (ROC) Curves. Values with $P \leq 0.05$ were accepted as statistically significant.

RESULTS

We included 114 patients into our study and the mean age of the patients was 53.75 ± 10.63 years.) Patients had endometrial endometrioid carcinoma (n = 71, 62.28%),

BH (n = 22, 19.3%), and EIN (n = 21, 18.42%). FOXA1 values were significantly higher in endometrial endometrioid carcinoma compared to the other groups ($p < 0.001$). Additionally, FOXA1 values were found to be significantly correlated with age ($r = 0.465$ $p < 0.001$).

Most of the carcinomas were nuclear grade 2 (n = 40, 56.34%) while 17 (23.94%) carcinomas were grade 1 and 14 (19.72%) carcinomas were grade 3 (Fig. 1). Carcinomas with nuclear grade 3 had higher FOXA1 values than others, and grade 2 had higher values than grade 1 ($p < 0.001$). Thirty-three (46.48%) carcinomas were histological grade 1, 31 (43.66%) grade 2, and 7 (9.86%) grade 3. Akin to nuclear grade, those with higher histological grade had higher FOXA1 values ($p < 0.001$). When we evaluated FIGO stage, we found that 28 (39.44%) carcinomas were stage I, 29 (40.85%) were stage II, and 14 (19.72%) were stage III. The FOXA1 values of our patients demonstrated a significant increase with each grade ($p < 0.001$, Fig. 2).

Twenty-three patients had myometrial invasion and these patients had significantly higher FOXA1 values compared to those without ($p < 0.001$). The most common invasion pattern was well-circumscribed invasion (44.44%). Ten patients had lymphovascular, eight cervical and six lymph node invasion. There were no significant differences for FOXA1 values regarding the invasion pattern, and the presence or absence of lymphovascular or cervical invasion. Patients with lymph node invasion had significantly higher FOXA1 values than those without ($p = 0.047$) (Tab. 1).

When we evaluated the capability of FOXA1 expression for the prediction of myometrial invasion, we found that FOXA1 had 91.3% sensitivity, 63.6% specificity and 77.78% accuracy for predicting the presence of myometrial invasion with a cut-off value of 9 (Tab. 2).

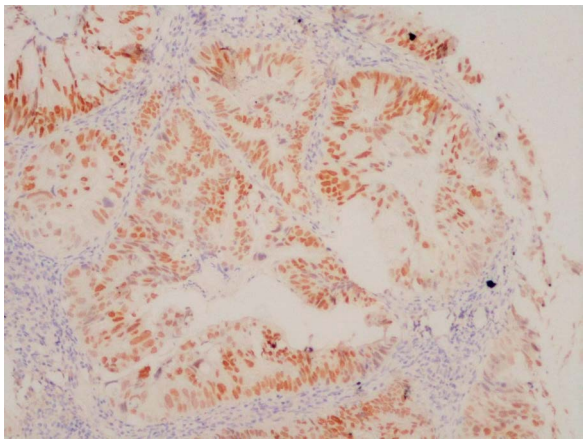

Figure 1. FOXA1 expression pattern in endometrial carcinoma: A strongly positive immunohistochemical staining (x 40)

DISCUSSION

The present study shows that patients with endometrial endometrioid carcinoma have higher FOXA1 expression compared to those with BH or EIN. Furthermore, FOXA1 expression was significantly increased in patients with higher grade endometrial endometrioid cancer. In addition, higher FOXA1 expression was found to be associated with tumor invasion.

FOXA1, a member of the FOX family of transcription factors, is acknowledged as a modulator of estrogen receptors in breast and androgen receptors in prostate cancer. Studies focused on breast cancer have revealed that FOXA1 triggers not only the development but also the progression of the disease, and it is essential for both estrogen receptor activity and its expression [14]. In addition, overexpression of FOXA1 has been suggested to prevent metastatic progression, either by altering the expression of BRCA1 -associated cell cycle inhibitor or directly stimulating transcription of the E-cadherin gene (CDH1), which results in the induction of E-cadherin expression and decreases the migration of cancer cells [15]. This dual action in breast cancers may indicate that FOXA1 may promote progression in the early stages of the tumor but suppresses progression in advanced stage.

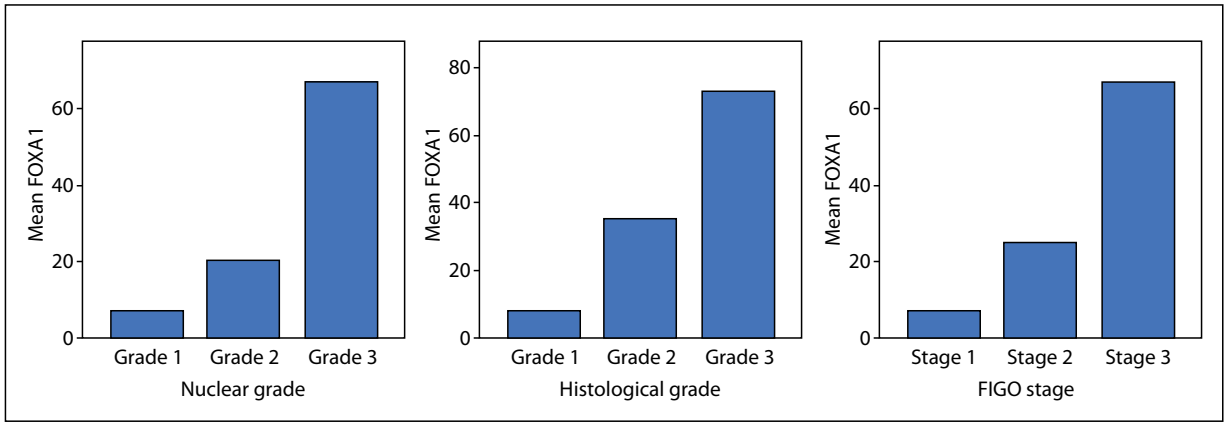

Figure 2. Figure demonstrating increasing FOXA1 expression levels with increasing tumor grade and FIGO stage

Table 1. Assessment of FOXA1 expression with regard to clinicopathological characteristics

		n	FOXA1 Expression (%)		
			Mean ± SD	Median (Min–Max)	p
Age (years)	≤ 55	53	11.57 ± 21.43	3 (0–90)	< 0.001
	> 55	61	21.84 ± 24.63	10 (0–90)	
Diagnosis	BH[a]	22	0.95 ± 2.42	0 (0–10)	< 0.001
	EIN[a]	21	2.00 ± 3.26	0 (0–10)	
	ECa[b]	71	26.51 ± 25.67	20 (0–90)	
Nuclear Grade (ECa)	Grade 1[a]	17	7.18 ± 5.04	5 (2–20)	< 0.001
	Grade 2[b]	40	20.50 ± 16.50	17.5 (0–60)	
	Grade 3[c]	14	67.14 ± 17.94	60 (45–90)	
Histological Grade (ECa)	Grade 1[a]	33	8.06 ± 4.80	6 (0–20)	< 0.001
	Grade 2[b]	31	35.68 ± 22.19	25 (8–90)	
	Grade 3[b]	7	72.86 ± 17.04	70 (50–90)	
FIGO Stage (ECa)	Stage I[a]	28	7.71 ± 4.58	6 (0–20)	< 0.001
	Stage II[b]	29	25.03 ± 17.22	20 (5–60)	
	Stage III[c]	14	67.14 ± 17.94	60 (45–90)	
Myometrial Invasion	Absent	22	12.27 ± 13.52	6 (2–50)	< 0.001
	Present	23	37.30 ± 28.57	25 (5–90)	
Invasion Patterns	Well-circumscribed	20	22.50 ± 21.45	15 (2–70)	0.640
	Diffusely Stromal	8	29.38 ± 30.41	17.5 (5–90)	
	Adenomyosis-like	10	22.50 ± 27.99	9 (5–85)	
	MELF	7	31.14 ± 31.56	20 (8–90)	
Lymphovascular Invasion	Absent	35	23.14 ± 24.86	10 (2–90)	0.116
	Present	10	31.80 ± 28.39	20 (8–90)	
Cervical Invasion	Absent	37	22.92 ± 24.31	10 (2–90)	0.102
	Present	8	35.00 ± 30.71	20 (10–90)	
Lymph Node Invasion	Absent	39	22.26 ± 23.73	10 (2–90)	0.047
	Present	6	43.33 ± 32.04	45 (10–90)	

Same letters denote lack of significant differences between groups. BH — benign endometrioid hyperplasia, ECa — endometrioid carcinoma, MELF — micro cystic, elongated and fragmented pattern

Table 2. FOXA1 Expression in Predicting Presence of Myometrial Invasion

Cut-off value	9
Sensitivity	91.30%
Specificity	63.60%
Positive predictive value	72.41%
Negative predictive value	87.50%
Diagnostic accuracy	77.78%
Area under ROC curve	0.842 ± 0.059
p	< 0.001

In breast cancer, FOXA1 expression has been demonstrated to be associated with various clinicopathological features and favorable outcomes including overall survival, breast cancer-specific survival, and relapse-free survival [16–18]. In contrast to breast cancer, FOXA1 expression is associated with reactivation of androgen receptor which plays a critical role in the development and progression of prostate cancer [19]. Overexpression of FOXA1 has been shown to be a predictor for poor outcome in prostate cancer [20].

Endometrial endometrioid cancer is nearly identical to breast cancer regarding the role of estrogen receptors, as estrogen receptor expression has been reported as a powerful prognostic marker [21]. In a preliminary study investigating FOXA1 expression in 109 cases with endometrial cancer, Abe et al. [22], found that FOXA1 expression was negatively associated with lymph node status. Moreover, exogenous FOXA1 application has been reported to sup-

press both the proliferation and migration of endometrial cancer cells [22]. Recently, Tangen et al., investigated the role of FOXA1 expression in a larger population including 529 primary and 199 metastatic endometrial carcinoma lesions and found that low FOXA1 levels were associated with a worse prognosis among estrogen receptor -negative patients. However, in those with estrogen receptor positivity, five-year survival was similar in patients with low or high FOXA1 expression [23]. In contrast to the findings of previous studies, our results indicate that FOXA1 expression is associated with high tumor grade, lymph node invasion and myometrial invasion. This inconsistency may be due to the recruitment of patients with endometrial endometrioid cancer where estrogen receptor expression is common. In addition, several studies have demonstrated that the majority of endometrial carcinomas also express androgen receptors in addition to estrogen receptors. Qiu et al. [24], in their study which evaluated 76 endometrial cancer specimens, demonstrated that FOXA1 expression was significantly correlated with androgen receptor expression, which was higher in advanced grade endometrial cancer, suggesting that FOXA1 might promote cell proliferation through androgen receptors. In other words, the interaction between androgen receptors and FOXA1 might be the actual cause of tumor proliferation in endometrial cancer; thus, providing an explanation to our results which were in contrast with most of the literature. Therefore, we speculate that the impact of FOXA1 on the development and progression of endometrial endometrioid carcinoma may be associated with the differences in the expression of estrogen and androgen receptors.

We believe that further studies are warranted to determine the exact mechanism by which FOXA1 impacts lymph node and myometrial invasion. Nevertheless, our results indicate that FOXA1 levels are associated with increased tumor grade and lymph node invasion which are conflicting with some of the results of previous research.

There are some limitations to be mentioned concerning the present study. These data must be interpreted with caution because of the relatively low sample size and the few number of patients enrolled with endometrial endometrioid carcinoma. Due to the lack of the follow-up, we could not provide data regarding the survival rates. In addition, we could not investigate estrogen and androgen receptor expressions in our samples, which may have provided further data to determine the effects of FOXA1 on disease progression; however, it is commonly acknowledged that endometrial endometrioid carcinomas estrogen receptor-positive tumors. Although we could obtain limited information from our scarce number of study patients, we believe that our findings will point to a critical role for FOXA1 in endometrial endometrioid cancer.

CONCLUSIONS

FOXA1 expression is higher in patients with endometrial endometrioid carcinoma compared to those with BH or EIN. In patients with endometrial endometrioid carcinoma, high FOXA1 expression is associated with high tumor grade, myometrial invasion and lymph node invasion. However, we have found no association between FOXA1 expression and cervical or lymphovascular invasion. Considering the conflicting results in the literature and the interesting characteristics of FOXA1 expression, we have indicated that further studies are needed to elucidate the role of FOXA1 in endometrial endometrioid carcinoma.

Funding

This study had no financial support.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012; 62(1): 10–29, doi: 10.3322/caac.20138, indexed in Pubmed: 22237781.
2. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO--ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer. 2016; 26(1): 2–30, doi: 10.1097/IGC.0000000000000609, indexed in Pubmed: 26645990.
3. Lortet-Tieulent J, Ferlay J, Bray F, et al. International Patterns and Trends in Endometrial Cancer Incidence, 1978-2013. J Natl Cancer Inst. 2018; 110(4): 354–361, doi: 10.1093/jnci/djx214, indexed in Pubmed: 29045681.
4. Banas T, Juszczyk G, Pitynski K, et al. Incidence and mortality rates in breast, corpus uteri, and ovarian cancers in Poland (1980-2013): an analysis of population-based data in relation to socioeconomic changes. Onco Targets Ther. 2016; 9: 5521–5530, doi: 10.2147/OTT.S112187, indexed in Pubmed: 27660470.
5. Sorosky J. Endometrial Cancer. Obstetrics & Gynecology. 2012; 120(2, Part 1): 383–397, doi: 10.1097/aog.0b013e3182605bf1.
6. Russo M, Broach J, Sheldon K, et al. Clonal evolution in paired endometrial intraepithelial neoplasia/atypical hyperplasia and endometrioid adenocarcinoma. Hum Pathol. 2017; 67: 69–77, doi: 10.1016/j.humpath.2017.07.003, indexed in Pubmed: 28712776.
7. Prat J, Gallardo A, Cuatrecasas M, et al. Endometrial carcinoma: pathology and genetics. Pathology. 2007; 39(1): 72–87, doi: 10.1080/00313020601136153, indexed in Pubmed: 17365824.
8. Huet-Hudson YM, Chakraborty C, De SK, et al. Estrogen regulates the synthesis of epidermal growth factor in mouse uterine epithelial cells. Mol Endocrinol. 1990; 4(3): 510–523, doi: 10.1210/mend-4-3-510, indexed in Pubmed: 2342484.
9. Carroll JS, Liu XS, Brodsky AS, et al.. Chromosome-wide mapping of estrogen receptor binding reveals long-range regulation requiring the forkhead protein FoxA1. Cell 2005; 122: 33-43.
10. Badve S, Turbin D, Thorat MA, et al. FOXA1 expression in breast cancer--correlation with luminal subtype A and survival. Clin Cancer Res. 2007; 13: 4415-21. doi: 10.1158/1078-0432.CCR-07-0122, indexed in Pubmed: 17671124
11. Gerhardt J, Montani M, Wild P, et al. FOXA1 promotes tumor progression in prostate cancer and represents a novel hallmark of castration-resistant prostate cancer. Am J Pathol. 2012; 180(2): 848–861, doi: 10.1016/j.ajpath.2011.10.021, indexed in Pubmed: 22138582.
12. Jin HJ, Zhao JC, Ogden I, et al. Androgen receptor-independent function of FoxA1 in prostate cancer metastasis. Cancer Res. 2013; 73(12): 3725–3736, doi: 10.1158/0008-5472.CAN-12-3468, indexed in Pubmed: 23539448.
13. Creasman W. Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet. 2009; 105(2): 109, doi: 10.1016/j.ijgo.2009.02.010, indexed in Pubmed: 19345353.

14. Wolf I, Bose S, Williamson EA, et al. FOXA1: Growth inhibitor and a favorable prognostic factor in human breast cancer. Int J Cancer. 2007; 120(5): 1013–1022, doi: 10.1002/ijc.22389, indexed in Pubmed: 17163418.
15. Hu Q, Luo Z, Xu T, et al. FOXA1: a promising prognostic marker in breast cancer. Asian Pac J Cancer Prev. 2014; 15(1): 11–16, doi: 10.7314/apjcp.2014.15.1.11, indexed in Pubmed: 24528009.
16. Hisamatsu Y, Tokunaga E, Yamashita N, et al. Impact of FOXA1 expression on the prognosis of patients with hormone receptor-positive breast cancer. Ann Surg Oncol. 2012; 19(4): 1145–1152, doi: 10.1245/s10434-011-2094-4, indexed in Pubmed: 21984487.
17. Mehta RJ, Jain RK, Leung S, et al. FOXA1 is an independent prognostic marker for ER-positive breast cancer. Breast Cancer Res Treat. 2012; 131(3): 881–890, doi: 10.1007/s10549-011-1482-6, indexed in Pubmed: 21503684.
18. Ijichi N, Shigekawa T, Ikeda K, et al. Association of double-positive FOXA1 and FOXP1 immunoreactivities with favorable prognosis of tamoxifen--treated breast cancer patients. Horm Cancer. 2012; 3(4): 147–159, doi: 10.1007/s12672-012-0111-0, indexed in Pubmed: 22476979.
19. Zhao Yu, Tindall DJ, Huang H. Modulation of androgen receptor by FOXA1 and FOXO1 factors in prostate cancer. Int J Biol Sci. 2014; 10(6): 614–619, doi: 10.7150/ijbs.8389, indexed in Pubmed: 24948874.
20. Sahu B, Laakso M, Ovaska K, et al. Dual role of FoxA1 in androgen receptor binding to chromatin, androgen signalling and prostate cancer. EMBO J. 2011; 30(19): 3962–3976, doi: 10.1038/emboj.2011.328, indexed in Pubmed: 21915096.
21. Salvesen HB, Haldorsen IS, Trovik J. Markers for individualised therapy in endometrial carcinoma. Lancet Oncol. 2012; 13(8): e353–e361, doi: 10.1016/S1470-2045(12)70213-9, indexed in Pubmed: 22846840.
22. Abe Y, Ijichi N, Ikeda K, et al. Forkhead box transcription factor, forkhead box A1, shows negative association with lymph node status in endometrial cancer, and represses cell proliferation and migration of endometrial cancer cells. Cancer Sci. 2012; 103(4): 806–812, doi: 10.1111/j.1349--7006.2012.02201.x, indexed in Pubmed: 22313737.
23. Tangen IL, Krakstad C, Halle MK, et al. Switch in FOXA1 status associates with endometrial cancer progression. PLoS One. 2014; 9(5): e98069, doi: 10.1371/journal.pone.0098069, indexed in Pubmed: 24849812.
24. Qiu M, Bao W, Wang J, et al. FOXA1 promotes tumor cell proliferation through AR involving the Notch pathway in endometrial cancer. BMC Cancer. 2014; 14: 78, doi: 10.1186/1471-2407-14-78, indexed in Pubmed: 24512546.